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FILE 'HOME' ENTERED AT 13:53:51 ON 24 MAR 2005

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FILE 'AGRICOLA' ENTERED AT 13:54:08 ON 24 MAR 2005

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FILE 'IMSDRUGCONF' ENTERED AT 13:54:08 ON 24 MAR 2005

FILE 'LIFESCI' ENTERED AT 13:54:08 ON 24 MAR 2005

FILE 'MEDICONF' ENTERED AT 13:54:08 ON 24 MAR 2005

FILE 'PASCAL' ENTERED AT 13:54:08 ON 24 MAR 2005

=> (malaria or plasmodium) and (nitrosothiol or nitrocysteine or nitrosoglutathione or cysteine)

L1	11	FILE AGRICOLA
L2	210	FILE BIOTECHNO
L3	5	FILE CONFSCI
L4	0	FILE HEALSAFE
L5	0	FILE IMSDRUGCONF
L6	216	FILE LIFESCI
L7	0	FILE MEDICONF
L8	112	FILE PASCAL

TOTAL FOR ALL FILES
L9 554 (MALARIA OR PLASMODIUM) AND (NITROSOTHIOL OR NITROCYSTEINE OR NITROSOGLUTATHIONE OR CYSTEINE)

=> l9 and (inhale or inhalation)

L10	0	FILE AGRICOLA
L11	0	FILE BIOTECHNO
L12	0	FILE CONFSCI
L13	0	FILE HEALSAFE

L14 0 FILE IMSDRUGCONF
L15 0 FILE LIFESCI
L16 0 FILE MEDICONF
L17 0 FILE PASCAL

TOTAL FOR ALL FILES
L18 0 L9 AND (INHALE OR INHALATION)

=> (malaria or plasmodium) and (nitrosothiol or nitrocysteine or nitrosoglutathione or cysteine or arginine) and (inhale or inhalation or inhaled)
L19 0 FILE AGRICOLA
L20 0 FILE BIOTECHNO
L21 0 FILE CONFSCI
L22 0 FILE HEALSAFE
L23 0 FILE IMSDRUGCONF
L24 0 FILE LIFESCI
L25 0 FILE MEDICONF
L26 0 FILE PASCAL

TOTAL FOR ALL FILES
L27 0 (MALARIA OR PLASMODIUM) AND (NITROSOTHIOL OR NITROCYSTEINE OR NITROSOGLUTATHIONE OR CYSTEINE OR ARGININE) AND (INHALE OR INHAL ATION OR INHALED)

cytokine-inducible **nitric oxide** synthase (iNOS) in spleen. **Treatment** of these mice with anti-IL-12 or anti-IFN-γ led to the progression of parasitemia and fatal outcome. Anti-IL-12 **treatment** significantly reduced the secretion and mRNA expression of IFN-γ and greatly diminished the augmentation of iNOS mRNA expression. In addition, recombinant IL-12 administration delayed the onset of parasitemia because of the enhanced IFN-γ production. These results suggest that blood-stage P. berghei XAT infection induces IL-12 production, which is important for the development of host resistance via IFN-γ production.

L62 ANSWER 22 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2000:100200 LIFESCI
TITLE: **Nitric oxide** inhibits the development of **Plasmodium** yoelii gametocytes into gametes
AUTHOR: Cao, Ya-Ming; Tsuboi, T.; Torii, M.*
CORPORATE SOURCE: Department of Parasitology, Ehime University School of Medicine, Shigenobu-cho, Ehime 791-0295, Japan; E-mail: torii@m.ehime-u.ac.jp
SOURCE: Parasitology International [Parasitol. Int.], (19980600) vol. 47, no. 2, pp. 157-166.
ISSN: 1383-5769.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The infectivity of gametocytes to the mosquito vector decreases dramatically during the early phase of plasmodial infection despite an increase in the number of gametocytes. The present study was aimed to clarify the mechanism of this natural transmission-blocking by using the murine **malaria** parasite, **Plasmodium** yoelii. The development of cultured gametocytes taken from the mice on days 4 and 5 after infection was significantly impaired; however, gametocytes taken from the mice on day 3 developed normally into ookinetes. These results indicated that the gametocyte infectivity was already lost in the infected host. The contribution of **nitric oxide** to diminished gametocyte infectivity was confirmed using L-NMMA, a selective inhibitor of **nitric oxide** synthase, and NOC5, a **nitric oxide** donor. The reduction of oocyst formation was partially reversed on day 4 after P. yoelii infection in the L-NMMA-treated group. The prevalence of infection among mosquitoes fed on mice 5 days after P. yoelii infection increased dramatically by the L-NMMA **treatment**. Moreover, the number of oocysts per mosquito midgut fed on the NOC5-treated mice infected with P. yoelii significantly decreased; likewise, gamete/zygote formation in vitro was inhibited by the pre-incubation of gametocytes with NOC5 before the gametogenesis. These results suggest that **nitric oxide**, as an effector molecule, inhibits the development of P. yoelii gametocytes into gametes.

L62 ANSWER 23 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1997:27398155 BIOTECHNO
TITLE: **Inhibition** of **nitric oxide** interrupts the accumulation of CD8.sup.+ T cells surrounding **Plasmodium** berghei-infected hepatocytes
AUTHOR: Scheller L.F.; Green S.J.; Azad A.F.
CORPORATE SOURCE: A.F. Azad, Maryland Univ. School of Medicine, Dept. of Microbiology/Immunology, Baltimore, MD 21201, United States.
SOURCE: Infection and Immunity, (1997), 65/9 (3882-3888), 31 reference(s)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27398155 BIOTECHNO

AB The elimination of liver-stage **malaria** parasites by **nitric oxide** (NO)-producing hepatocytes is regulated by T cells. Both CD8.sup.+ and CD4.sup.+ T cells, which surround infected hepatocytes, are evident by 24 h after sporozoite challenge in Brown Norway rats previously immunized with irradiated **Plasmodium** berghei sporozoites. While the number of CD4.sup.+ T cells remained the same beyond 24 h postchallenge, the number of CD8.sup.+ T cells increased three- and sixfold by 31 and 44 h, respectively. This increase in the number of CD8.sup.+ T cells correlated with a decrease in the number of intrahepatic parasites. In immunized rats, intrahepatic parasites were reduced in number by 31 h after sporozoite challenge and cleared from the liver by 44 h, as visualized by P. berghei- specific DNA in situ hybridization. If immunized rats were treated with aminoguanidine, a substrate inhibitor of NO synthase, at the time of challenge, liver-stage protection was blocked, as shown by the increase in parasite liver burden. Further histological examination of infected livers from immunized animals treated with aminoguanidine revealed fewer and smaller cellular infiltrates surrounding the infected hepatocytes, and the number of CD8.sup.+ T cells that normally accumulate within the infiltrates was drastically reduced. Consequently, the infected hepatocytes were not cleared from the liver. We hypothesize that the early production of NO may promote the influx and/or enhance local proliferation of **malaria** parasite-specific CD8.sup.+ T cells or a CD8.sup.+ T-cell subset which is required for parasite clearance.

L62 ANSWER 24 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 97:114544 LIFESCI
TITLE: Complete protective immunity induced in mice by immunization with the 19-kilodalton carboxyl-terminal fragment of the merozoite surface protein-1 (MSP1 sub(19)) of **Plasmodium** yoelii expressed in Saccharomyces cerevisiae. Correlation of protection with antigen-specific antibody titer, but not with effector CD4 super(+) T cells
AUTHOR: Hirunpetcharat, C.; Tian, Jing-Hui; Kaslow, D.C.; Van Rooijen, N.; Kumar, S.; Berzofsky, J.A.; Miller, L.H.; Good, M.F.*
CORPORATE SOURCE: Queensland Inst. Med. Res., P.O. Royal Brisbane Hosp., Brisbane 4029, Australia
SOURCE: J. IMMUNOL., (19971000) vol. 159, no. 7, pp. 3400-3411. ISSN: 0022-1767.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The 19-kDa carboxyl-terminal fragment of the merozoite surface protein-1 (MSP1) is a leading **malaria** vaccine candidate but is unable to induce immunity in all monkeys or all strains of mice. The mechanism of immunity is unclear, although data show that cell-mediated immunity plays a critical role following immunization with the larger mature MSP1 protein. We optimized a vaccine protocol using the MSP1 sub(19) fragment of **Plasmodium** yoelii expressed in Saccharomyces cerevisiae, such that following exposure of mice to parasites, they remained undetectable in peripheral blood, whereas control animals all died at very high parasitemia within 10 days. We then depleted the vaccinated mice of >99% of CD4 super(+) T cells by anti-CD4 mAb **treatment** and could show that infections in most animals remained subpatent following challenge. Furthermore, mice in which the gene for the mu -chain of Ig had been disrupted could not be immunized with MSP1 sub(19). Immunity in normal mice did not depend on the presence of an intact spleen nor production of **nitric oxide**, persisting unabated when >70% of splenic macrophages were depleted. Thus, while effector CD4 super(+) T cells may contribute to immunity, neither they nor factors associated with a Th1-type cell mediated immune response appeared to play the major role in MSP1 sub(19)-induced protection in normal mice. Furthermore, T cells were not sufficient for immunity in mice lacking B cells. In normal mice, protection correlated with a very high titer of MSP1 sub(19)-specific Abs (>6,400,000), predominantly G1 and G2b, which may function by merozoite neutralization.

L62 ANSWER 25 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 1998:82438 LIFESCI
TITLE: Upregulation of reactive oxygen and nitrogen intermediates in **Plasmodium** berghei infected mice after rescue therapy with chloroquine or artemether
AUTHOR: Prada, J.; Mueller, S.; Bienzle, U.; Kremsner, P.G.*
CORPORATE SOURCE: Sektion Humanparasitologie, Institut fuer Tropenmedizin, Universitaet Tuebingen Wilhelmstrasse 27, D-72074, Tuebingen, Germany
SOURCE: J. ANTIMICROB. CHEMOTHER., (19960700) vol. 38, no. 1, pp. 95-102.
ISSN: 0305-7453.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Plasmodium** berghei ANKA infected C57B1/6 mice develop cerebral **malaria** at a parasitaemia of 15-25%. When parasitaemia reached 10%, P. berghei infected mice were treated with artemether, chloroquine or clindamycin in order to prevent the occurrence of cerebral **malaria**. Artemether and chloroquine were highly efficient. Functional tests revealed that zymosan stimulated spleen cells from untreated mice with cerebral **malaria** showed a slight decrease in their capacity to produce reactive oxygen intermediates (ROI) when compared with naive mice. After artemether or chloroquine **treatment**, the ROI production was significantly enhanced. The interferon-gamma induced production of reactive nitrogen intermediates (RNI) was slightly elevated in mice with cerebral **malaria**, but markedly elevated in artemether or chloroquine treated mice when compared with naive mice. Moreover, high levels of inducible **nitric oxide** synthase gene expression could be detected by in-situ hybridization in spleen sections of mice which had been treated with artemether or chloroquine. These findings suggest that increased production of ROI and RNI after chemotherapy may play a protective role for the host during **malaria**.

synthase gene that's all

L62 ANSWER 26 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1996:26009339 BIOTECHNO
TITLE: In vivo regulation of **nitric oxide** production by tumor necrosis factor alpha and gamma interferon, but not by interleukin-4, during blood stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, McGill University, Montreal General Hosp. Res. Inst., 1650 Cedar Ave.,Montreal, Que. H3G 1A4, Canada.
SOURCE: Infection and Immunity, (1996), 64/1 (44-49)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26009339 BIOTECHNO
AB We investigated whether gamma interferon (IFN-γ; a Th1 cytokine), tumor necrosis factoe alpha (TNF-α), and interleukin-4 (IL-4; a Th2 cytokine) modulate **nitric oxide** (NO) production in vivo during blood stage infection with **Plasmodium** chabaudi AS. **Treatment** of resistant C57BL/6 mice, which resolve infection with P. chabaudi AS and produce increased levels of IFN- γ, TNF-α, and NO early during infection, with anti-IFN-γ plus anti-TNF-σ monoclonal antibodies (MAbs) resulted in a reduction of both splenic inducible NO synthase mRNA and serum NO.sub.3.sup.- levels by 50 and 100%, respectively. **Treatment** with the anti-TNF-α MAb alone reduced only serum NO.sub.3.sup.- levels by 35%, and **treatment** with the anti-IFN-γ MAb alone had no effect on NO production by these mice during infection. Susceptible A/J

mice, which succumb to infection with P. chabaudi AS and produce increased levels of IL-4 but low levels of IFN-γ, TNF-α, and NO early during infection, were treated with an anti-IL-4 MAb. The latter **treatment** had no effect on NO production by this mouse strain during infection. In addition, our results also demonstrate that **treatment** of resistant C57BL/6 mice with anti-IFN-γ plus anti-TNF-α MAbs affects, in addition to NO production, other traits of resistance to P. chabaudi AS **malaria** such as the peak level of parasitemia and the development of splenomegaly. Furthermore, the change in spleen weight was shown to be an IFN-γ-independent effect of TNF-α. **Treatment** of susceptible A/J mice during infection with an anti-IL-4 MAb had no effect on these markers of resistance. Thus, these results demonstrate that TNF-α and IFN-γ are critical in the regulation of NO production and other traits of resistance during P. chabaudi AS **malaria** in C57BL/6 mice. These data also indicate that **treatment** with an anti-IL-4 antibody alone is not able to induce NO production or confer resistance to A/J mice against P. chabaudi AS **malaria**.

L62 ANSWER 27 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1995:25353607 BIOTECHNO
TITLE: **Nitric oxide** expression in the spleen, but not in the liver, correlates with resistance to blood-stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada.
SOURCE: Journal of Immunology, (1995), 155/11 (5306-5313)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25353607 BIOTECHNO
AB The production and function of **nitric oxide** during the early phase of blood-stage infection with **Plasmodium** chabaudi AS was analyzed using two inbred strains of mice that differ in the level of resistance to this parasite. Northern blot analysis of in vivo expression of inducible **nitric oxide** synthase (iNOS) revealed that early during infection resistant C57BL/6 mice, which clear the infection by 4 wk, have higher levels of iNOS mRNA in the spleen than susceptible A/J mice. In contrast, susceptible A/J mice have significantly increased levels of iNOS mRNA in the liver later in the course of infection just before death occurs. Splenic macrophages recovered from resistant C57BL/6 mice on day 7 postinfection express iNOS mRNA which is up- regulated following overnight stimulation of the cells with LPS. Furthermore, during the first week postinfection, splenic macrophages recovered from resistant hosts produce significantly higher levels of nitrite (NO.sub.2.sup.-) in vitro in response to LPS than similarly stimulated macrophages from susceptible A/J mice. Increased levels of nitrate (NO.sub.3.sup.-) were only detected in serum of resistant C57BL/6 mice at the time of peak parasitemia. **Treatment** with the iNOS inhibitor, aminoguanidine, reduced NO.sub.3.sup.- levels in serum of C57BL/6 mice and eliminated resistance of these hosts to P. chabaudi AS **malaria** without affecting parasitemia. These results demonstrate that the ability to produce high amounts of **nitric oxide** (NO) early during infection with blood-stage P. chabaudi AS correlates with resistance, but that NO may not be involved in parasite **killing**. Moreover, the tissue site of NO production, that is, spleen vs liver, appears to be critical and correlates with resistance vs susceptibility to P. chabaudi AS **malaria**, respectively.

L62 ANSWER 28 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1995:25263620 BIOTECHNO
TITLE: IL-12-induced protection against blood-stage

Plasmodium chabaudi AS requires IFN-γ and TNF-α and occurs via a **nitric oxide**-dependent mechanism

AUTHOR: Stevenson M.M.; Mi Fong Tam; Wolf S.F.; Sher A.

CORPORATE SOURCE: Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada.

SOURCE: Journal of Immunology, (1995), 155/5 (2545-2556) CODEN: JOIMA3 ISSN: 0022-1767

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

AN 1995:25263620 BIOTECHNO

AB The effects of IL-12 administration on the development of protective immunity to blood-stage **Plasmodium** chabaudi AS were analyzed. **Treatment** of susceptible A/J mice on the day of infection and for 5 days postinfection with various doses (0.025-0.3 μg) of rIL-12 significantly decreased the peak parasitemia level, but only **treatment** with 0.1 μg resulted in increased survival. **Treatment** of resistant 86 mice with 0.1 μg of rIL-12 using the same regimen also significantly decreased the peak parasitemia level, but 40% of the animals died. **Treatment** of these mice with anti-IL-12 mAb resulted in a more severe course of infection, but survival was not significantly altered. The mechanism of IL-12-induced resistance was examined in A/J mice during infection. Compared with spleen cells from untreated mice, cells from IL-12-treated mice produced significantly higher levels of IFN-γ spontaneously as well as in response to Con A or Ag stimulation on day 7 postinfection. Significantly higher levels of IFN-γ and TNF-α were found in the sera of IL-12-treated mice, which correlated with high levels of the **nitric oxide** (NO) metabolite, NO.sub.3.sup.-. Furthermore, CD4.sup.+ T cell depletion was found to abrogate IL-12-induced resistance. Administration of neutralizing mAb against IFN-γ or TNF-α to IL-12-treated mice showed that simultaneous depletion of both cytokines resulted in 100% mortality. The role of NO was investigated by administration of aminoguanidine, a selective inhibitor of cytokine-inducible **nitric oxide** synthase, to IL-12-treated mice. Significantly increased mortality was observed following **treatment** twice daily with 9 mg of aminoguanidine, but there was no effect on parasitemia. In conclusion, these results demonstrate that IL-12 regulates the development of resistance to P. chabaudi AS via a CD4.sup.+ Th1 response, which involves the cytokines IFN-γ and TNF-α, and is in part NO dependent. Therefore, IL-12, given in the appropriate dose, may be useful in the induction of protective immunity to blood-stage **malaria**.

L62 ANSWER 29 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN

ACCESSION NUMBER: 97:45603 LIFESCI

TITLE: The heme moiety of **malaria** pigment (beta -hematin) mediates the **inhibition** of **nitric oxide** and tumor necrosis factor alpha production by lipopolysaccharide-stimulated macrophages

AUTHOR: Taramelli, D.; Basilico, N.; Pagani, E.; Grande, R.; Monti, D.; Ghione, M.; Olliaro, P.

CORPORATE SOURCE: Istituto di Microbiologia Medica, Univ. di Milano, Via Pascal 36, 20133 Milano, Italy

SOURCE: EXP. PARASITOL., (1995) vol. 81, no. 4, pp. 501-511. ISSN: 0014-4894.

DOCUMENT TYPE: Journal

FILE SEGMENT: K

LANGUAGE: English

SUMMARY LANGUAGE: English

AB To investigate the effect of the heme moiety of **malaria** pigment, hemozoin, on phagocyte functions, mouse macrophages were fed with insoluble beta -hematin, the synthetic heme-polymer chemically identical to the native pigment, or the soluble monomer, hematin. Production of inflammatory cytokines, interleukin 1 (IL1), tumor necrosis factor alpha

(TNF alpha), and **nitric oxide** (NO) was assayed in the supernatants after stimulation with lipopolysaccharide. The results indicate that both beta -hematin and hematin induce a dose-dependent **inhibition** of macrophage production of TNF alpha and NO, but not of IL1. One-hour pretreatment with soluble hematin inhibited production of cytotoxic mediators by more than 50% compared to controls, while 6-hr exposure was necessary for insoluble beta -hematin to induce the same level of **inhibition**. However, the same **treatment** did not modify the production of TNF alpha and NO by mouse microglia cell lines. The **inhibition** was partially counterbalanced by adding sulphydryl group donors such as 2-mercaptoethanol, glutathione, or N-acetyl-cysteine during the preincubation time. The results of the present study confirm the inhibitory role of **malaria** pigment and show that such effect is due to the heme moiety and may be selective for the production of cytotoxic mediators by specific phagocytes. The implications of these findings in the control of **malaria** infection and disease and in the pathogenesis of severe **malaria** are discussed.

L62 ANSWER 30 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:24264354 BIOTECHNO
TITLE: **Nitric oxide**-mediated antiplasmodial activity in human and murine hepatocytes induced by gamma interferon and the parasite itself: Enhancement by exogenous tetrahydrobiopterin
AUTHOR: Mellouk S.; Hoffman S.L.; Liu Z.-Z.; De la Vega P.; Billiar T.R.; Nussler A.K.
CORPORATE SOURCE: Chirurgie I, Chirurgische Forschung, Universitaet Ulm, Parkstrasse II,89073 Ulm, Germany.
SOURCE: Infection and Immunity, (1994), 62/9 (4043-4046)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:24264354 BIOTECHNO
AB Expression of inducible **nitric oxide** (NO) synthase has been shown to inhibit the development of several pathogens, including fungi, bacteria, parasites, and viruses. However, there is still controversy as to whether this effector mechanism can inhibit the development of human pathogens. We now report that gamma interferon (IFN-γ) induces the elimination of **Plasmodium** falciparum-infected primary human hepatocytes from cultures and that the antimalarial activity is dependent on NO. Infection with the parasite alone in the absence of added IFN-γ caused a 10-fold increase in NO formation. Both spontaneous **inhibition** and IFN-γ-induced **inhibition** of **Plasmodium** yoelii-infected murine hepatocytes were increased with the addition of the NO synthase cofactor tetrahydrobiopterin, or sepiapterin, which is converted to tetrahydrobiopterin. These results indicate that under in vitro conditions the parasite itself provides a signal that triggers induction of the NO pathway in human and murine hepatocytes and that NO formation in infected hepatocytes is limited by tetrahydrobiopterin availability.

L62 ANSWER 31 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1994:24279473 BIOTECHNO
TITLE: Effector mechanisms against asexual erythrocytic stages of **Plasmodium**
AUTHOR: Phillips S.
CORPORATE SOURCE: Department of Zoology, University of Glasgow,Glasgow G12 2QQ, Scotland, United Kingdom.
SOURCE: Immunology Letters, (1994), 41/2-3 (109-114)
CODEN: IMLED6 ISSN: 0165-2478
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Netherlands
LANGUAGE: English

SUMMARY LANGUAGE: English
AN 1994:24279473 BIOTECHNO
AB Evidence for a role for macrophages/monocytes is largely based on in vitro not in vivo observations. Products of activated macrophages particularly tumor necrosis factor-alpha (TNFα) are implicated in the **killing** of parasites. Access of cytokines and other factors might be through intracellular channels in the infected red blood cell. The cytotoxic elements in 'crisis' serum are uncertain but may include TNF, gamma-interferon (IFNγ), and lipid peroxidases. TNFα in excess, contributes to pathology. TNF, acting as a pyrogen and raising body temperature, may moderate parasite density by **killing** late asexual stages. **Nitric oxide** and other nitrogen intermediates, products of activated macrophages and a number of other cell types, have been demonstrated both in vitro and in vivo to have a protective role. Phagocytosis of infected erythrocytes and merozoites, enhanced by the presence of immune serum in some systems, has been reported. **Killing** of parasites by neutrophils is enhanced by immune serum and cytokines TNFα, IFNγ and lymphotoxin. A role for natural killer cells has been suggested. Evidence for antibody-dependent cellular cytotoxicity (ADCC) is controversial. Antibody-dependent cellular inhibitory activity (ADCI) (blood monocytes plus immune IgG) has been described for P. falciparum. Evidence for an important role for complement is conflicting; an involvement in the protective activity of phagocytic cells is reported. Antibody isotypes have been relatively little studied. In murine systems IgG(2a) may have a role early in the protective immune response followed by IgG.sub.1. In P. falciparum ADCI activity is mediated by IgG.sub.1 and IgG.sub.3, two cytophilic isotypes. Antigenic variation by the asexual erythrocytic stages has been described for a number of **malaria** species and appears to serve as an immune evasion mechanism. One variant antigen has been located on the surface of trophozoite/schizont-infected erythrocytes and may be involved in cytoadherence. In P. falciparum in vitro and P. chabaudi in vivo antigenic switching may be at the rate of 2% per generation.

L62 ANSWER 32 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:25009346 BIOTECHNO
TITLE: **Nitric Oxide**: Cytokine-regulation of **nitric oxide** in host resistance to intracellular pathogens
AUTHOR: Green S.J.; Scheller L.F.; Marletta M.A.; Seguin M.C.; Klotz F.W.; Slayter M.; Nelson B.J.; Nacy C.A.
CORPORATE SOURCE: EntreMed, Inc.,Rockville, MD, United States.
SOURCE: Immunology Letters, (1994), 43/1-2 (87-94)
CODEN: IMLED6 ISSN: 0165-2478
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:25009346 BIOTECHNO
AB To discover how **nitric oxide** (NO) synthesis is controlled in different tissues as cells within these tissues combat intracellular pathogens, we examined three distinctively different experimental murine models designed for studying parasite-host interactions: macrophage **killing** of Leishmania major; nonspecific protection against tularemia (Francisella tularensis) by Mycobacterium bovis (BCG); and specific vaccine-induced protection against hepatic **malaria** with **Plasmodium** berghei. Each model parasite and host system provides information on the source and role of NO during infection and the factors that induce or inhibit its production. The in vitro assay for macrophage antimicrobial activity against L. major identified cytokines involved in-regulating NO-mediated **killing** of this intracellular protozoan. zoan. L. major induced the production of two competing cytokines in infected macrophages: (1) the parasite activated the gene for tumor necrosis factor (TNF), and production of TNF protein was enhanced by the presence of interferon-gamma (IFN-γ). TNF then acted as a autocrine signal to amplify IFN-γ-induced production of NO, and (2) the parasite

upregulated production of transforming growth factor-beta (TGF-β), which blocked IFN-γ-induced production of NO. Whether parasite-induced TNF (parasite destruction) or TGF-β (parasite survival) prevailed depended upon the presence and quantity of IFN-γ at the time of infection. The relationship between NO production in vivo and host resistance to infection was demonstrated with M. bovis (BCG). These studies confirmed that both IFN-γ and TNF are required for induction of NO-mediated nonspecific host defense in vivo. The presumed source of NO in these studies was the activated macrophage, however, other cells infected with parasites can also be stimulated to produce NO. In studying acquired immunity to **malaria** induced by irradiated sporozoites, we found that IFN-γ provided by **malaria**-specific CD8.sup.+ T cells stimulated sporozoite-infected hepatocytes to produce NO for destruction of either infected hepatocytes or the parasite, P. berghei, within these cells.

L62 ANSWER 33 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 93:53793 LIFESCI
TITLE: Interferon- gamma induced lethality in the late phase of **Plasmodium** vinckei **malaria** despite effective parasite clearance by chloroquine.
AUTHOR: Kremsner, P.G.; Neifer, S.; Chaves, M.F.; Rudolph, R.; Bienzle, U.
CORPORATE SOURCE: Landesinst. Tropenmed. Berlin, Engeldamm 62, 1020 Berlin, FRG
SOURCE: EUR. J. IMMUNOL., (1992) vol. 22, no. 11, pp. 2873-2878.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A combination therapy was tested consisting of chloroquine and interferon-gamma (IFN- gamma) in the late phase of blood-stage **Plasmodium** vinckei **malaria** in BALB/c mice. Pretreatment of P. vinckei -infected mice with pentoxifylline, a phosphodiesterase inhibitor, led to a significant decrease of IFN- gamma -induced lethality. In contrast, pretreatment with neutralizing antibodies to tumor necrosis factor or with L-N-monomethyl arginine, the latter an inhibitor of the **nitric oxide** synthase, significantly increased lethality.

L62 ANSWER 34 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 93:61277 LIFESCI
TITLE: **Nitric oxide** and cerebral **malaria**.
AUTHOR: Senaldi, G.; Kremsner, P.G.; Grau, G.E.
CORPORATE SOURCE: WHO Immunol. Res. and Train. Cent., Dep. Pathol., Univ. Geneva, 1211 Geneva, Switzerland
SOURCE: LANCET., (1992) vol. 340, no. 8834-8835, p. 1554.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
AB Dr. Clark and colleagues draw attention to features shared by cerebral **malaria**, heat stroke, postoperative transitory syndrome, and the neurological syndrome that may develop as a result of **treatment** with tumour necrosis factor (TNF) or interleukin-2 (IL-2). Some features (mental disturbances such as coma and seizures, and high concentrations of circulating proinflammatory cytokines such as TNF and IL-1) are reversible in non-fatal cases; but, cerebral **malaria**, for example, is invariably lethal if untreated. Clark and colleagues postulate that **nitric oxide** (NO) represents the physiopathological link between mental disturbances and cytokine concentrations: cytokines would induce the synthesis of NO in the vascular wall of the brain circulation, which would then diffuse into the brain parenchyma and affect neurological function. We present experimental data that do not support this view.

L62 ANSWER 35 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 91:11939 LIFESCI
TITLE: IFN- gamma inhibits development of **Plasmodium** berghei exoerythrocytic stages in hepatocytes by an

L-arginine-dependent effector mechanism.
AUTHOR: Mellouk, S.; Green, S.J.; Nacy, C.A.; Hoffman, S.L.
CORPORATE SOURCE: Malar. Program, Nav. Med. Res. Inst., 12300 Washington Ave., Rockville, MD 20852, USA
SOURCE: J. IMMUNOL., (1991) vol. 146, no. 11, pp. 3971-3976.
DOCUMENT TYPE: Journal
FILE SEGMENT: K; F
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Primary cultures of BALB/cJ hepatocytes treated with 10 super(3) U/ml rIFN- gamma consistently inhibited intracellular **Plasmodium** berghei) liver schizont development by 50 to 70%. Monomethyl-L-arginine (N super(G)MMLA), the competitive inhibitor of L-arginine as substrate for production of **nitric oxides** by hepatocytes, reversed the activity of IFN- gamma on these **malaria**-infected cells. The data strongly suggest that the action of IFN- gamma on P. berghei)-infected hepatocytes is to induce the production of L-arginine-derived nitrogen oxides that are toxic for the intracellular parasite.

L62 ANSWER 36 OF 37 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1991:21280985 BIOTECHNO
TITLE: **Killing** of **Plasmodium** falciparum in vitro by **nitric oxide** derivatives
AUTHOR: Rockett K.A.; Awburn M.M.; Cowden W.B.; Clark I.A.
CORPORATE SOURCE: Division of Cell Biology, John Curtin Med. Research Sch., Australian National University,Canberra, ACT 2601, Australia.
SOURCE: Infection and Immunity, (1991), 59/9 (3280-3283)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Note
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1991:21280985 BIOTECHNO
AB We have investigated the in vitro susceptibility of the human **malaria** parasite **Plasmodium** falciparum to **killing** by **nitric oxide** and related molecules. A saturated solution of **nitric oxide** did not inhibit parasite growth, but two oxidation products of **nitric oxide** (nitrite and nitrate ions) were toxic to the parasite in millimolar concentrations. Nitrosothiol derivatives of cysteine and glutathione were found to be about a thousand times more active (50% growth inhibitory concentration, approximately 40 μM) than nitrite.

L62 ANSWER 37 OF 37 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 1998:27774 LIFESCI
TITLE: Tumour necrosis factor and associated cytokines in the host's response to **malaria**
AUTHOR: Richards, A.L.
CORPORATE SOURCE: U.S. Naval Med. Res. Unit No. 2, Box 3, U.S. Embassy Jakarta, APO, AP 96520-8132, USA
SOURCE: pp. 1251-1263.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Tumour Necrosis Factor (TNF) is produced at the initiation of **malaria** infections (pre-erythrocytic phase), as demonstrated by the release of bioactive TNF by peripheral blood mononuclear cells from individuals residing in endemic areas after stimulation with stage specific sporozoite antigens. During the erythrocytic phase, TNF production is greatly augmented by parasite antigens at the time of schizont rupture and merozoite release from infected erythrocytes. Some of the strongest inducers of TNF synthesis and release are **malaria** toxins, e.g. glycosylphosphatidylinositol moieties and **malaria**

pigment. Because of TNF's well-known cytotoxic activity it was originally hypothesized that it alone was responsible for **killing** parasites directly or within host cells. Though earlier reports of the capability of serum containing TNF to kill **plasmodia** supported this idea, later experiments with recombinant TNF showed a lack of significant parasiticidal activity. Recent studies investigating related factors showed that they were involved with TNF in the control of infection. These factors included other cytokines, such as interleukin (IL)-1, IL-6, IL-12, interferon-gamma (IFN gamma) as well as **nitric oxide** intermediates (NOI) and reactive oxygen intermediates (ROI). This positioned TNF as a key regulator of the immune response against the **malaria** parasite. However, it must be noted that TNF and its associated factors are also responsible for the fever, aches and pains of acute illness, as well as the hypoglycemia, shock, bleeding and reversible coma of severe **malaria** seen in approximately 1 percent of individuals with **malaria**. Therein lies the rub; factors important in the control of **malaria** also appear to have detrimental properties. Research presented in this review characterizes TNF and associated cytokines' importance in the immune response to **malaria**.

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